Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 4-10, 17, 18, 20-46, 48-57, 150-153, 155-157, 165, 166 and 171-175 are pending in the application, with claims 1, 150 and 166 being the independent claims. Claims 2, 3, 11-16, 19, 47, 58-149, 154, 158-164 and 167-170 are sought to be cancelled. Claim 175 is sought to be added. Claims 1, 4-8, 10, 21, 26, 29, 54, 55, 57, 150, 151, 153, 156, 166 and 171-174 are sought to be amended to more clearly describe that which Applicants claim as their invention. Support for the definition of prodrug can be found, *inter alia*, on page 15, lines 7-23 of the application as filed. Support for nucleotide as a possible M can be found, *inter alia*, on page 60, line 23 through page 61, line 5. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Interview Summary

Applicants representatives, John Lucas, Esq., Dr. Scott Hecker and Robert W. Esmond, Esq., met with the Examiner April 20, 2005 for a personal interview. In the interview, the pending claims of the present application were discussed. It was agreed that the term prodrug would be defined in the claims. Also, the proviso for FPBase inhibitors would be removed, and the method claims would be amended by adding an additional step. Finally, Applicants would submit references showing phosphate, or

similar, containing drugs along with the current Reply. Agreement was reached on the above amendments, and agreement on the claims was withheld pending filing of the Reply.

II. Rejections Under 35 U.S.C. § 112

A. The Radical M (Office Action Sections 3-5)

1. Definiteness

Claims 1-3, 7, 9, 11-18, 20-46, 48-53, 56, 150-153, 155-157, 165, 166 and 171-173 were rejected under 35 U.S.C. § 112, second paragraph. *See* Office Action, section 3 (page 2, line 20, through page 3, line 6). Applicants respectfully traverse the rejection.

"The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent." M.P.E.P. § 2173 (May 2004). Applicants can use any terms they choose, so long as a term is clearly set forth in the specification. *Id.* § 2173.01. The Examiner should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness. *Id.* § 2173.02.

Independent claims 1, 150 and 166 are directed to prodrugs of phosphate or phosphonate containing parent drugs (M attached to hydrogen, i.e. MH, or M attached to phosphorous, i.e. M-PO_3^{2-}) and methods of making the same. Formula I structurally defines these prodrugs. The radical M is also defined in the claims and relates to phosphate or phosphonate parent drugs that are biologically active agents. See, the specification at page 20, lines 22-28. Because the subject matter of claims 1, 150 and 166 is clear when read in light of the specification, the claims are definite.

In addition, phosphate or phosphonate containing parent drugs, and drugs that are phosphorylated *in vivo*, are well known in the art and are readily identifiable. To demonstrate this, by way of example, Applicants have attached Appendices A and B to this Reply. Appendix A lists representative examples of drugs containing phosphate, or similar, groups. Appendix B lists representative examples of drugs that are phosphorylated *in vivo* (The Examiner's attention is directed to the "Mechanism of Action" section for each drug in Appendix B describing the phosphorylation).

The representative examples were derived from the *Physician's Desk Reference* ("PDR"), a well known reference on approved drugs, and Prous Science Integrety®, a well known, searchable, on-line database for drugs and biologics.[1]

One of ordinary skill in the art would recognize that these representative drugs can be used in the present invention. Appendices A and B include, by way of example, nucleoside analogs, sulfonamides, bisphosphonates, corticoid steroids, and other types of structurally defined phosphate containing drugs and drugs that are phosphorylated *in vivo*. By referring to well known references such as the PDR or the Integrety® database, and by reading the specification, one of ordinary skill in the art would understand what a parent drug is, and therefore, how the radical M is defined. Thus, the definition for the parent drug and M are reasonable in light of what is known in the art and the teachings of the specification.

For at least these reasons, the subject matter of claims 1, 150 and 166 define the radical M with reasonable clarity and are definite. And since claims 4-10, 17, 18, 20-46, 48-57, 150-153, 155-157, 165, 166 and 171-175 depend from these claims, and are also

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[1] Prous Science, and the Integrety® database, are available on-line at http://www.prous.com/ (last accessed June 9, 2005).

reasonably clear, these claims are also definite. Applicants request that the rejection be withdrawn.

2. Written Description

Claims 1-3, 7, 9-18, 20-46, 48-53, 150-153, 155-157, 165, 166 and 171-173 were rejected under 35 U.S.C. § 112, first paragraph. *See* Office Action, section 4 (page 3, line 14, through page 7, line 7). Applicants respectfully traverse the rejection.

Applicant's invention is directed to prodrugs linked to biologically active agents through a phosphorous in Formula I via a carbon, oxygen, sulfur or nitrogen atom. Once such prodrugs have been shown to work for one drug, it can be applied to other drugs that contain the same functional group, i.e. linked through a phosphorous in Formula I via a carbon, oxygen, sulfur or nitrogen atom. Applicants' invention is not *per se* the discovery of biologically active agents.

There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. M.P.E.P. § 2163 I.A. (May 2004).

An Applicant may show possession of an invention in a variety of ways including . . . describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention. *Id.* § 2163 II.A.3.(a).

Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. Recitation of functional characteristics in a claim does not render the claim per se as not in compliance with the written description requirement.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species. See M.P.E.P. § 2163

II.A(3)(ii). What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. *Id.*

The present specification sets forth a multitude of representative species of the claimed genus, and the level of skill and knowledge in the art is very high. Thus, under the USPTO's guidelines, the written description requirement is fully satisfied for the claimed subject matter.

The specification literally teaches thousands of compounds having Formula I. *See* pages 71-88 and the examples. The specification also teaches numerous classes of biologically active agents and gives examples for each class. *See* pages 44-45. The specification also lists a large number of nucleosides that are biologically active agents according to the present invention. *See* pages 60-65. This large number of representative species satisfies the written description requirement.

For at least the above reasons, Applicants submit that claims 1, 7, 9, 10, 17, 18, 20-46, 48-53, 150-153, 155-157, 165, 166 and 171-173 satisfy the written description requirement and request that the rejection be withdrawn.

3. Enablement

Claims 1-3, 7, 9-18, 20-46, 48-53, 150-153, 155-157, 165, 166 and 171-173 were rejected under 35 U.S.C. § 112, first paragraph. *See* Office Action, section 5 (page 7, line 8, through page 13, line 13). Applicants respectfully traverse the rejection.

The invention relates to the discovery of a new class of prodrugs that may be applied to biologically active agents in a general sense. Given a biologically active agent, one can form a prodrug of Formula I from a parent drug (M-H or M-PO_3^{2-}) without undue experimentation. In fact, numerous specific examples of methods of preparing prodrugs attached to biologically active agents are disclosed. See pages 89-98,

generally, and Examples 1-13 (pages 103-115). Applicants' invention is not the discovery of biologically active agents but rather new prodrugs that can be applied to the same functional group in other biologically active agents. One can make such prodrugs based upon Applicant's disclosure with no more than routine experimentation.

In addition, one of ordinary skill in the art could identify biologically active agents that would work under the conditions taught by the specification. Submitted herewith, in addition to this Reply, is an Information Disclosure Statement listing numerous references that teach biologically active substances containing phosphate or similar functional groups, or substances that are phosphorylated. Also included are references describing drugs which are phosphorylated *in vivo*. This listing supplements that of the specification and represents examples of biologically active substances known at the time of the present invention. The agents can be used as such in the methods of the present invention to produce prodrugs that fall within the scope of claim 1.

B. Prodrug (Office Action, Sections 6-8)

Claims 1-18, 20-46, 48-57, 150-153, 155-157, 165 and 171-174 were rejected under 35 U.S.C. § 112, second paragraph. *See* Office Action, section 6 (page 13, line 15, through page 14, line 3). Applicants respectfully traverse the rejection

Claims 1, 150, 171, 172 and 173 has been amended to recite the meaning of the term prodrug. The remaining claims are dependent on one of the amended independent claims. Because the claims now recite the meaning of the term prodrug, Applicants respectfully submit that the rejection has become moot and request that it be withdrawn.

Claims 1-3, 7, 9-18, 20-46, 48-53, 150-153, 155-157, 165, 166 and 171-174 were rejected under 35 U.S.C. § 112, first paragraph. *See* Office Action, sections 7 and 8 (page 14, line 4, through page 20, line 9). Applicants respectfully traverse the rejection.

As discussed above, the rejected claims have been amended to recite the meaning of the term prodrug. Applicants submit the amendments render the rejections moot, and request that they be withdrawn.

C. The Negative Proviso (Office Action, Section 9)

Claims 1-3, 7, 9-18, 20-46, 48-53, 150-153, 155-157, 165, 166 and 171-174 were rejected under 35 U.S.C. § 112, second paragraph. *See* Office Action, section 9 (page 20, line 11, through page 21, line 11). Applicants respectfully traverse the rejection.

The negative proviso, referred to by the Examiner in the rejection, has been cancelled from the claims. Applicants submit the rejection is now moot and request that it be withdrawn.

III. Rejection Under 35 U.S.C. § 112 and 35 U.S.C. § 101

Process Claim 150 (Office Action, Section 10)

Claim 150 was rejected under 35 U.S.C. § 112, second paragraph and under 35 U.S.C. § 101. *See* Office Action, section 10 (page 21, line 13, through page 24, line 13). Applicants respectfully traverse the rejection.

Claim 150 now recites an active step in the method of preparing the compounds of Formula I. Applicants submit this amendment renders moot the rejection and request that it be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant(s) therefore respectfully request(s) that the Examiner reconsider all presently outstanding objections and rejections and that they be

withdrawn. Applicant(s) believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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